

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75025

APPROVAL LETTER

JUL 23 1998

Taylor Pharmaceuticals
Attention: James G. Baumann, Jr.
1222 West Grand Avenue
Decatur, Illinois 62525

Dear Sir:

This is in reference to your abbreviated new drug application dated December 12, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lorazepam Injection USP, 2 mg/mL (vial).

Reference is also made to your amendments dated August 27, 1997; and March 2, May 18, June 9, and July 7 and July 16, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Lorazepam Injection USP, 2 mg/mL (1 mL vial) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ativan® Injection USP, 2 mg/mL of Wyeth Ayerst Laboratories Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director

Office of Generic Drugs
Center for Drug Evaluation and Research

Sporn

7-23-82

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

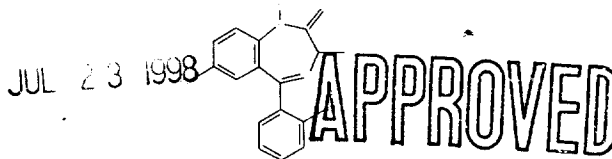
APPLICATION NUMBER:
75025

DRAFT FINAL PRINTED LABELING

Lorazepam Injection, USP

DESCRIPTION

Lorazepam Injection, USP is a sterile solution. Lorazepam is a benzodiazepine with anxiolytic and sedative effects intended for intramuscular or intravenous routes of administration. It has the following chemical name: 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one. The molecular formula is $C_{15}H_{10}Cl_2N_2O$. The molecular weight is 321.16, and the C.A.S. No. is [846-49-1]. The structural formula is:



Lorazepam is a nearly white powder almost insoluble in water.

Each mL contains: Active: Lorazepam 2 mg. **Preservative:** Benzyl alcohol 20 mg. **Inactives:** 203 mg polyethylene glycol 400 in propylene glycol.

CLINICAL PHARMACOLOGY

Lorazepam interacts with the γ -aminobutyric acid (GABA)-benzodiazepine receptor complex, which is widespread in the brain of humans as well as other species. This interaction is presumed to be responsible for lorazepam's mechanism of action. Lorazepam exhibits relatively high and specific affinity for its recognition site but does not displace GABA. Attachment to the specific binding site enhances the affinity of GABA for its receptor site on the same receptor complex. The pharmacodynamic consequences of benzodiazepine agonist actions include anxiolytic effects and sedation. The intensity of action is directly related to the degree of benzodiazepine receptor occupancy.

Effects in Pre-Operative Patients

Intravenous or intramuscular administration of the recommended dose of 2 mg to 4 mg of lorazepam injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety, and lack of recall of events related to the day of surgery in the majority of patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that the majority of patients are able to respond to simple instructions whether they give the appearance of being awake or asleep. The lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. The majority of patients under these reinforced conditions had difficulty recalling perioperative events or recognizing props from before surgery. The lack of recall and recognition was determined under conditions of careful patient questioning and testing, using props designed to enhance recall. The majority of patients under these reinforced conditions had difficulty recalling perioperative events or recognizing props from before surgery. The lack of recall and recognition was optimum within 2 hours following intramuscular administration and 15 to 20 minutes after intravenous injection.

The intended effects of the recommended adult dose of lorazepam injection usually last 6 to 8 hours. In rare instances and where patients received greater than the recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Physiologic Effects in Healthy Adults

Studies in healthy adult volunteers reveal that intravenous lorazepam in doses up to 3.5 mg/70 kg produces no significant sensitivity to the respiratory stimulating effect of carbon dioxide and does not enhance the respiratory depressant effects of doses of isopentidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway compromise has been observed in rare instances when the patient received greater than the recommended dose and/or received other drugs and fluids (see WARNINGS and ADVERSE REACTIONS).

Clinically employed doses of lorazepam injection do not greatly affect the oculovestibular system in the supine position employing a 30-degree tilt test. Doses of 8 mg to 10 mg of intravenous lorazepam 2 mg/mL benzodiazepine injection, recommended dosage, will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and 10 chloral hydrate tablets (100 mg each) tracking the ability to keep a moving time centered was reported for a mean of 10.8 seconds. Following intramuscular administration of 4 mg of intramuscular lorazepam and 10 chloral hydrate tablets, the mean time centered was 12.2 seconds with considerable subject variation. Similar findings were noted when a water load of 1500 cc was ingested. Although this study showed that both lorazepam and pentobarbital interfered with performance of a tracking task, it is insufficient to predict when it would be safe to operate a motor vehicle or engage in other hazardous activities.

Pharmacokinetics and Metabolism

Absorption

Intravenous

A 4 mg dose provides an initial concentration of approximately 70 ng/mL.

Intramuscular

Following intramuscular administration, lorazepam is completely and rapidly absorbed. In healthy volunteers, within 3 hours, a 4 mg dose provides a C_{max} of approximately 48 ng/mL. Following intramuscular administration,

lorazepam (ME) the amount of lorazepam delivered to the circulation is proportional to the dose administered.

Distribution-Metabolism-Excretion

At clinically relevant concentrations, lorazepam is 91 \pm 2% bound to plasma proteins; its volume of distribution is approximately 1.3 L/kg. Unbound lorazepam penetrates the blood-brain barrier freely by passive diffusion, a fact corroborated by a M. singhline. Following parenteral administration, the terminal half-life and total clearance averaged 14.5 hours and 1.1 \pm 0.4 mL/min/kg, respectively.

Lorazepam is extensively conjugated to the 3-O phenolic glucuronide in the liver and is known to undergo enterohepatic recirculation. Lorazepam glucuronide is an inactive metabolite and is eliminated mainly by the kidneys.

Following a single 2-mg oral dose of ¹⁴C-lorazepam to healthy subjects, 88 \pm 4% of the administered dose was recovered in urine and 7 \pm 2% was recovered in feces. The percent of administered dose recovered in urine as lorazepam glucuronide was 74 \pm 4%. Only 0.3% of the dose was recovered as unchanged lorazepam, and the remainder of the radioactivity represented minor metabolites.

Special Populations

Effect of Age

Pediatrics

Neonates (Birth to 2 months)

Following a single 0.05 mg/kg (n=4) or 0.1 mg/kg (n=6) intravenous dose of lorazepam, mean total clearance normalized to body weight was reduced by 50% compared to normal adults; terminal half-life was prolonged 3-fold, and volume of distribution was decreased by 40% in neonates with asphyxia neonatorum compared to normal adults. All neonates were of < 37 weeks of gestational age.

Infants (2 months up to 2 years)

There is no information on the pharmacokinetic profile of lorazepam in infants in the age range of 1 month to 2 years.

Children (2 years to 12 years)

Total bound and unbound lorazepam had a 50% higher mean volume of distribution (normalized to body weight) and a 30% longer mean half-life in children with acute lymphocytic leukemia in complete remission (2-12 years, n=12) compared to normal adults (n=10). Unbound lorazepam clearance normalized to body weight was comparable in children and adults.

Adolescents (12 years to 18 years)

Total bound and unbound lorazepam had a 50% higher mean volume of distribution (normalized to body weight) and a mean half-life that was two-fold greater in adolescents with acute lymphocytic leukemia in complete remission (12-18 years, n=13) compared to normal adults (n=10). Unbound lorazepam clearance normalized to body weight was comparable in adolescents and adults.

Elderly

Following single intravenous doses of 1.5-3 mg of lorazepam injection, mean total body clearance of lorazepam decreased by 20% in 18 elderly subjects (of 60-84 years of age compared to that in 18 younger subjects of 19-38 years of age. Consequently, no dosage adjustment appears to be necessary in elderly subjects based solely on their age.

Effect of Gender

Gender has no effect on the pharmacokinetics of lorazepam.

Effect of Race

Young Americans (n=18) and Japanese subjects (n=7) had very comparable mean total clearance value of 1.0 mL/min/kg. However, elderly Japanese subjects had a 20% lower mean total clearance than elderly Americans, 0.59 mL/min/kg vs. 0.77 mL/min/kg, respectively.

Patients with Renal Insufficiency

Because the kidneys is the primary route of elimination of lorazepam glucuronide, renal impairment would be expected to compromise its clearance. This should have no direct effect on the glucuronidation (and metabolism) of lorazepam. There is possibility that the enterohepatic circulation of lorazepam glucuronide leads to a reduced clearance of the total clearance of lorazepam in this population.

Seventeen elderly patients with renal impairment (5 of 72-84 and four patients on chronic hemodialysis) were given single 0.5-3 mg intravenous doses of lorazepam. Mean volume of distribution and terminal half-life values of lorazepam were dose- and age-related, respectively, in renally impaired patients and normal subjects. Both parameters were 75% higher in patients undergoing hemodialysis than in normal subjects. In spite of the mean half-life of 14.5 hours, the mean total clearance of lorazepam did not change when compared to normal subjects (1.1 mL/min/kg) as much as total lorazepam during the 2-hour dosing session.

Clearance of lorazepam glucuronide was also decreased in these elderly patients. The mean terminal half-life was increased to 45 and 178 hours in elderly out-patients and patients under hemodialysis, respectively, as compared to normal subjects. The mean terminal half-life was increased by 78% and 160% in renally impaired patients and patients on hemodialysis, respectively, as compared to normal subjects. About 40% of the administered lorazepam was excreted in the urine as lorazepam glucuronide in the 2-hour dosing session.

Hepatic

Because the kidneys is the primary route of elimination of lorazepam glucuronide, liver disease would not be expected to compromise its clearance. This prediction is supported by the observation that following single 2-mg intravenous doses of lorazepam, the mean terminal half-life was not significantly different in elderly patients with mild to moderate liver disease and normal adult subjects (n=14) as compared to normal subjects (n=10) who had no liver disease.

Other Special Populations

Administration of lorazepam to elderly patients with lorazepam showed that there is no difference in any of the pharmacokinetic parameters of lorazepam between the two groups. Elderly patients over 65 and non-elderly patients under 65 were given single intravenous doses of lorazepam.

INDICATIONS AND USAGE

Preanesthetic

Lorazepam is indicated for sedation in adult patients undergoing anesthesia and for pre-sedation (anxiolysis).

or drowsiness, relief of anxiety and a decreased ability to recall events related to the day of surgery. It is most useful in those patients who are anxious about their surgical procedure and who would prefer to have diminished recall of the events of the day of surgery (see "PRECAUTIONS - Information for Patients").

CONTRAINDICATIONS

Lorazepam injection is contraindicated in patients with a known sensitivity to benzodiazepines or its vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) and in patients with acute narrow-angle glaucoma. The use of lorazepam injection intra-arterially is contraindicated because, as with other injectable benzodiazepines, such use may produce arteriospasm, resulting in gangrene which may require amputation (see "WARNINGS").

WARNINGS

Preanesthetic Use

PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. INTRAVENOUS LORAZEPAM, WHEN GIVEN ALONE IS GREATER THAN THE RECOMMENDED DOSE, OR AT THE RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING THE ADMINISTRATION OF ANESTHESIA, MAY PRODUCE HEAVY SEDATION. THEREFORE, EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY AND TO SUPPORT RESPIRATION/VENTILATION SHOULD BE AVAILABLE.

As is true of similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or engage in hazardous occupations or drive a motor vehicle for a period of 24 or 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, concomitant use of other drugs, stress of surgery, or the general condition of the patient.

Clinical trials have shown that patients over the age of 50 years may have a more profound and prolonged sedation with intravenous lorazepam. Ordinarily, an initial dose of 2 mg may be adequate unless a greater degree of lack of recall is desired.

As with all central-nervous-system depressant drugs, care should be exercised in patients given injectable lorazepam as premature ambulation may result in injury from falling.

There is no added beneficial effect from the addition of scopolamine to injectable lorazepam, and their combined effect may result in an increased incidence of sedation, hallucination, and irrational behavior.

General (All Uses)

PRIOR TO INTRAVENOUS USE, LORAZEPAM INJECTION MUST BE DILUTED WITH AN EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE "DOSAGE AND ADMINISTRATION"). INTRAVENOUS INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CARE SHOULD BE TAKEN TO DETERMINE THAT ANY INJECTION WILL NOT BE INTRA-ARTERIAL AND THAT PERIVASCULAR EXTRAVASATION WILL NOT TAKE PLACE.

Since the liver is the most likely site of conjugation of lorazepam and since excretion of conjugated lorazepam glucuronide is a renal function, this drug is not recommended for use in patients with hepatic and/or renal failure. This does not preclude use of the drug in patients with mild to moderate hepatic or renal disease (See "DOSAGE AND ADMINISTRATION").

Pregnancy

LORAZEPAM MAY CAUSE FETAL DAMAGE WHEN ADMINISTERED TO PREGNANT WOMEN. Ordinarily, lorazepam injection should not be used during pregnancy except in serious or life-threatening conditions where safer drugs cannot be used or are ineffective.

An increased risk of congenital malformations associated with the use of minor tranquilizers (chloridiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. In humans, blood levels obtained from umbilical cord blood indicate placental transfer of lorazepam and lorazepam glucuronide.

There are insufficient data regarding obstetrical safety of parenteral lorazepam, including use in cesarean section. Such use, therefore, is not recommended.

Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional anomalies (reduction of tarsals, ribs, metatarsals, malrotated limbs, gastroschisis, malformed skull, and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all of these anomalies were not present in a concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg orally or 4 mg/kg intravenously and higher, there was evidence of fetal resorption and increased fetal loss on days which was not seen at lower doses.

Endoscopic Procedures

There are insufficient data to support the use of lorazepam injection for outpatient endoscopic procedures. Topical endoscopic procedures require adequate recovery from observations.

Pharyngeal reflexes are not impaired when lorazepam injection is used for premedication of endoscopic procedures; therefore, adequate topical or regional anesthesia is recommended to minimize patient anxiety associated with such procedures.

PRECAUTIONS

General

The additive central-nervous-system effects of other drugs, such as phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, and monoamine oxidase inhibitors, should be borne in mind when these other drugs are used concomitantly with or during the period of recovery from lorazepam injection (see "CLINICAL PHARMACOLOGY and WARNINGS").

Extreme care must be used in administering lorazepam to elderly patients, very ill patients, and to patients with reduced pulmonary reserve because of the possibility that underoxygenation and/or hypoxemic cardiac arrest may occur. Resuscitative equipment for ventilatory support should be readily available (see "WARNINGS" and "DOSAGE AND ADMINISTRATION").

When lorazepam injection is used IV as the premedication prior to general or local anesthesia, the possibility of

excessive sleepiness or drowsiness may interfere with patient cooperation to determine levels of anesthesia. This is most likely to occur when greater than 0.05 mg/kg is given and when narcotic analgesics are used concomitantly with the recommended dose (see "ADVERSE REACTIONS").

Information for Patients

As appropriate, the patient should be informed of the pharmacological effects of the drug, such as sedation, relief of anxiety, and lack of recall, and the duration of these effects (about 8 hours), so that they may adequately perceive the risks as well as the benefits to be derived from its use.

Patients who receive lorazepam as a premedicant should be cautioned that driving an automobile or operating hazardous machinery, or engaging in a hazardous sport, should be delayed for 24 to 48 hours following the injection. Sedatives, tranquilizers, and narcotic analgesics may produce a more prolonged and profound effect when administered along with injectable lorazepam. This effect may take the form of excessive sleepiness or drowsiness and, on rare occasions, interfere with recall and recognition of events of the day of surgery and the day after.

Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be consumed for at least 24 to 48 hours after receiving lorazepam injectable due to the additive effects on central-nervous-system depression seen with benzodiazepines in general. Elderly patients should be told that lorazepam may make them very sleepy for a period longer than six (6) to eight (8) hours following surgery.

Laboratory Tests

In clinical trials, no laboratory test abnormalities were identified with either single or multiple doses of lorazepam. These tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus, and total proteins.

Drug Interactions

Lorazepam injection, like other injectable benzodiazepines, produces depression of the central nervous system when administered with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors, and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam, an increased incidence of sedation, hallucinations, and irrational behavior has been observed.

Concurrent administration of any of the following drugs with lorazepam had no effect on the pharmacokinetics of lorazepam: metoprolol, cimetidine, ranitidine, disulfiram, propranolol, metronidazole, and propoxyphene. No change in lorazepam injection dosage is necessary when concomitantly given with any of these drugs.

Lorazepam - Valproate Interaction

Concurrent administration of lorazepam (2 mg intravenously) with valproate (250 mg twice daily orally for 3 days) to 6 healthy male subjects resulted in decreased total clearance of lorazepam by 40% and decreased formation rate of lorazepam-glucuronide by 55%, as compared with lorazepam administered alone. Accordingly, lorazepam plasma concentrations were about two-fold higher for at least 12 hours post-dose administration during valproate treatment. Lorazepam dosage should be reduced to 50% of the normal adult dose when this drug combination is prescribed in patients (see also "DOSAGE AND ADMINISTRATION").

Lorazepam-Oral Contraceptive Steroids Interaction

Coadministration of lorazepam (2 mg intravenously) with oral contraceptive steroids (norethindrone acetate, 1 mg, and ethinyl estradiol, 50 mcg, for at least 6 months) to healthy females (n=7) was associated with a 55% decrease in half-life, a 50% increase in the volume of distribution, thereby resulting in an almost 3.7-fold increase in total clearance of lorazepam as compared with control healthy females (n=8). It may be necessary to increase the doses of lorazepam injection in female patients who are concomitantly taking oral contraceptives (see also "DOSAGE AND ADMINISTRATION").

Lorazepam-Probenecid Interaction

Concurrent administration of lorazepam (2 mg intravenously) with probenecid (500 mg orally every 6 hours) to 9 healthy volunteers resulted in a prolongation of lorazepam half-life by 130% and a decrease in its total clearance by 45%. No change in volume of distribution was noted during probenecid co-treatment. Lorazepam injection dosage needs to be reduced by 50% when coadministered with probenecid (see also "DOSAGE AND ADMINISTRATION").

Drug/Laboratory Test Interactions

No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, such as narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and a variety of tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. The results of a preimplantation study in rats, in which the oral lorazepam dose was 20 mg/kg, showed no impairment of fertility.

Pregnancy

Pregnancy Category D

See "WARNINGS".

Labor and Delivery

There are insufficient data to support the use of lorazepam injection during labor and delivery, including cesarean section; therefore, its use in this situation is not recommended.

Nursing Mothers

Injectable lorazepam should not be administered to nursing mothers because, like other benzodiazepines, the possibility exists that lorazepam may be excreted in human milk and sedate the infant.

Pediatric Use

Preanesthetic

There are insufficient data to support the efficacy of injectable lorazepam as a preanesthetic agent in patients less than 18 years of age.

ADVERSE REACTIONS

Preanesthetic

Central Nervous System

The most frequent adverse effects seen with injectable lorazepam are an extension of the central nervous system depressant effects of the drug. The incidence varied from one study to another, depending on the dosage, route of administration, use of other central-nervous-system depressants, and the investigator's opinion concerning the degree and duration of desired sedation. Excessive sleepiness and drowsiness were the main side effects. This interfered with patient cooperation in approximately 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years of age had a higher incidence of excessive sleepiness or drowsiness when compared with those under 50 (21/106 vs 24/245) when lorazepam was given intravenously (see "DOSAGE AND ADMINISTRATION"). On rare occasion (3/1580) the patient was unable to give personal identification in the operating room on arrival, and one patient fell when attempting premature ambulation in the postoperative period.

Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself by picking at his incision during the immediate postoperative period.

Hallucinations were present in about 1% (14/1580) of patients and were visual and self-limiting.

An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during the peak effect period.

An occasional patient had a prolonged recovery room stay, either because of excessive sleepiness or because of some form of inappropriate behavior. The latter was seen most commonly when scopolamine was given concomitantly as a premedicant.

Limited information derived from patients who were discharged the day after receiving injectable lorazepam showed that one patient complained of some unsteadiness of gait and a reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages has been reported more than 24 hours after receiving injectable lorazepam similar to experience with other benzodiazepines.

Local Effects

Intramuscular injection of lorazepam has resulted in pain at the injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. The overall incidence of pain and burning in patients was about 17% (146/859) in the immediate postinjection period and about 1.4% (12/859) at the 24-hour observation time. Reactions at the injection site (redness) occurred in approximately 2% (17/859) in the immediate postinjection period and were present 24 hours later in about 0.8% (7/859).

Intravenous administration of lorazepam resulted in painful responses in 13/771 patients or approximately 1.6% in the immediate postinjection period, and 24 hours later, 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately following intravenous injection but was noted in 19/771 patients at the 24-hour observation period. This incidence is similar to that observed with an intravenous infusion before lorazepam is given.

Cardiovascular System

Hypertension (0.1%) and hypotension (0.1%) have occasionally been observed after patients received injectable lorazepam.

Respiratory System

Five patients (5/416) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at the time of the procedure and resulted in temporary underventilation. Immediate attention to the airway, employing the usual countermeasures, will usually suffice to manage this condition (see also "CLINICAL PHARMACOLOGY," "WARNINGS," and "PRECAUTIONS").

Other Adverse Experiences

Skin rash, nausea, and vomiting have occasionally been noted in patients who have received injectable lorazepam combined with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE

As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no clinical data available for injectable lorazepam in this respect, physicians should be aware that repeated use over a prolonged period of time may result in limited physical and psychological dependence.

Lorazepam Injection, USP is classified as a C-IV by the Drug Enforcement Administration.

OVERDOSAGE

Overdosage of benzodiazepines is usually manifested by varying degrees of central nervous system depression. Patient recovery shows a tendency toward a biphasic pattern including a period of arousal, confusion, and delirium, followed by a second period of depression. Symptoms may include ataxia, hypotension, depression, hypoxia, stupor, coma, and death. The clinical course may be fatal.

The most serious symptoms are respiratory depression and coma. The incidence of respiratory depression and coma is related to the dose of lorazepam administered. An overdose of 10 mg or more may result in severe respiratory depression and coma. When combined with other sedatives, the incidence of respiratory depression and coma is increased. The clinical course of overdosage may be fatal. The clinical course of overdosage may be fatal. The clinical course of overdosage may be fatal.

The most serious symptoms are respiratory depression and coma. The incidence of respiratory depression and coma is related to the dose of lorazepam administered. An overdose of 10 mg or more may result in severe respiratory depression and coma. When combined with other sedatives, the incidence of respiratory depression and coma is increased. The clinical course of overdosage may be fatal. The clinical course of overdosage may be fatal. The clinical course of overdosage may be fatal.

DOSAGE AND ADMINISTRATION

Preanesthetic

Intramuscular Injection

For the primary purpose of sedation and relief of anxiety, the usual recommended initial dose of lorazepam intramuscular injection is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice

injection is 0.05 mg/kg up to a maximum of 4 mg. As with all premedicant drugs, the dose should be individualized (See also "CLINICAL PHARMACOLOGY," "WARNINGS," "PRECAUTIONS," and "ADVERSE REACTIONS"). Doses of other central-nervous-system depressant drugs should be ordinarily reduced ("PRECAUTIONS"). For optimum effect, measured as lack of recall, intramuscular lorazepam should be administered at least 2 hours before the anticipated operative procedure. Narcotic analgesics should be administered at their usual preoperative time. There are insufficient data to support efficacy to make dosage recommendations intramuscular lorazepam in patients less than 18 years of age; therefore, such use is not recommended.

Intravenous Injection

For the primary purpose of sedation and relief of anxiety, the usual recommended initial dose of lorazepam intravenous injection is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice sedating most adult patients and should not ordinarily be exceeded in patients over 50 years of age. In those patients in whom a greater likelihood of lack of recall for postoperative events would be beneficial, larger doses as high as 0.05 mg/kg up to a total of 4 mg may be administered (see "CLINICAL PHARMACOLOGY," "WARNINGS," "PRECAUTIONS," and "ADVERSE REACTIONS"). Doses of other injectable central nervous system depressant drugs should ordinarily be reduced (see "PRECAUTIONS"). For optimum effect, measured as lack of recall, intravenous lorazepam should be administered 15 to 20 minutes before the anticipated operative procedure.

EQUIPMENT NECESSARY TO MAINTAIN A PATIENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO INTRAVENOUS ADMINISTRATION OF LORAZEPAM (see "WARNINGS").

There are insufficient data to support efficacy or make dosage recommendations for intravenous lorazepam in patients less than 18 years of age; therefore, such use is not recommended.

Administration

When given intramuscularly, lorazepam injection, undiluted, should be injected deep in the muscle mass.

Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants.

Immediately prior to intravenous use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing intravenous infusion. The rate of injection should not exceed 2 mg per minute.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Lorazepam Injection is compatible for dilution purposes with the following solutions: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; Dextrose Injection, USP, 5%.

DIRECTIONS FOR DILUTION FOR IV USE FOR PREFILLED SYRINGES

To dilute, adhere to the following procedure:

1. Extrude the entire amount of air in the half-filled syringe.
2. Slowly aspirate the desired volume of diluent.
3. Pull back slightly on the plunger to provide additional mixing space.
4. Immediately mix contents thoroughly by gently inserting syringe repeatedly until a homogeneous solution is obtained. Do not shake vigorously as this will result in an emulsion.

For oral

Aspirate the desired amount of lorazepam injection into the syringe, then proceed as described under "DIRECTIONS FOR DILUTION FOR IV USE FOR PREFILLED SYRINGES."

HOW SUPPLIED

Lorazepam Injection, USP is available as:

2 mg/ml (1 ml fill) in a 2 ml prefilled syringe, 22 gauge x 1 1/2 inch needle, NDC 11098-101-10.

2 mg/ml (1 ml fill) in a 2 ml vial, NDC 11098-102-10.

Lorazepam Injection, USP is for IM or IV injection.

STORAGE: Store in a refrigerator between 2° to 8° (36° to 46° F). Protect from light. Do not use if contents are discolored or contain a precipitate.

References

Taylor Pharmaceuticals

Decorah, IA 52003

© Taylor Pharmaceuticals, Inc. 1997

REMOVED

NDC 11099-122-01
2 mg/mL
Lorazepam
Injection, USP
1 mL, Sterile

FOR THE INJECTION
For IV use, additional
dilution is required, see
package information.

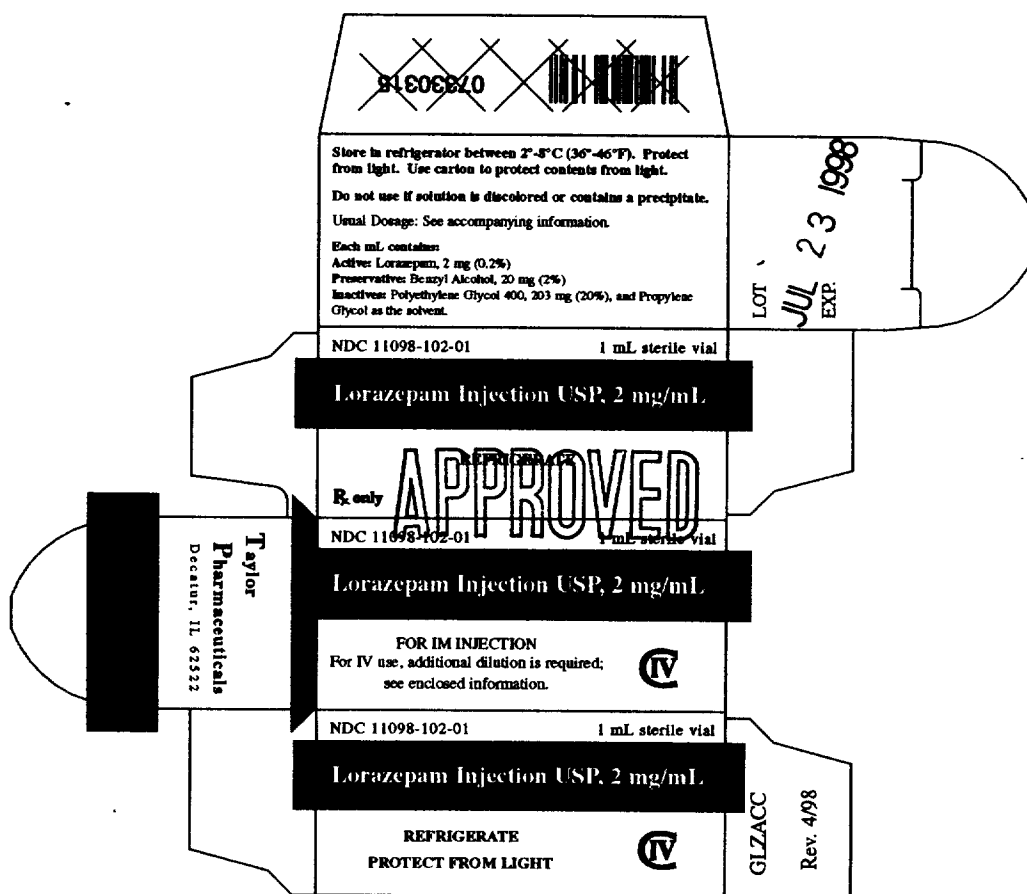
Store in refrigerator
between 2° and 8°C (36°
and 46°F). Do not freeze.
Protect from light. Do not
use if the solution is discolored or
contains particulate matter.
See USP Chapter 34,
Controlled Substances,
for handling information.

Rx only

Tyco Healthcare
Division, LLC
GILZACIL, Rev. 0188

LOT

23 198



91606820



Store in refrigerator between 2°-8°C (36°-46°F). Protect from light. Use carton to protect contents from light.

Do not use if solution is discolored or contains a precipitate.

Usual Dosage: See accompanying information.

Each mL contains:

Active: Lorazepam, 2 mg (0.2%)

Preservatives: Benzyl Alcohol, 20 mg (2%)

Inactives: Polyethylene Glycol 400, 203 mg (20%), and Propylene Glycol as the solvent.

LOT

JUL 23 1998
EXP:

NDC 11098-102-01

1 mL sterile vial

Lorazepam Injection USP, 2 mg/mL

Rx only

APPROVED

NDC 11098-102-01

1 mL sterile vial

Lorazepam Injection USP, 2 mg/mL

FOR IM INJECTION
For IV use, additional dilution is required;
see enclosed information.



NDC 11098-102-01

1 mL sterile vial

Lorazepam Injection USP, 2 mg/mL

REFRIGERATE
PROTECT FROM LIGHT



GLZACC

Rev. 4/98

Taylor
Pharmaceuticals
Decatur, IL 62522

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75025

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-025	CHEMIST: Kathy P. Woodland	DATE: July 8, 1998
DRUG PRODUCT: Lorazepam Injection, USP		
FIRM: Taylor Pharmaceuticals (Formerly Akorn, Inc.)		
DOSAGE FORM: Injection	STRENGTH: 0.2% ,2 mg/mL (1 ml/2 ml vial)	
cGMP: Satisfactory June 24, 1997.		
BIO: Satisfactory, Zakaria Z. Wahba , Ph.D., on June 6, 1997.		
VALIDATION - (Description of dosage form same as firm's): USP drug substance and product.		
STABILITY: The containers in the stability studies are identical to those in the container section.		
LABELING: Approved by L. Golson on May 26, 1998.		
STERILIZATION VALIDATION (If applicable): processing approved by Andrea High, Ph.D., March 10, 1998		
SIZE OF BIO BATCH (Firm's source of NDS ok?): Waiver granted.		
SIZE OF STABILITY BATCHES (If different from bio batch, were they Manufactured via the same process?): The exhibit batch was 20 L.		
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?: The proposed production batches are 36 L, 48 L and 100 L.		
Signature of chemist: <div style="text-align: center; font-size: 1.5em;">/S/</div>	Signature of supervisor: <div style="text-align: center; font-size: 1.5em;">/S/</div> <div style="text-align: right; font-family: cursive;">7/2/98</div>	

C:\WPFILES\APS\SUM750.WPD

- 1.
- CHEMISTRY REVIEW NO.
- 3

2. ANDA # 75-025 (1 mL/2 mL vial)

3. NAME AND ADDRESS OF APPLICANT

Taylor Pharmaceuticals (Formerly Akorn, Inc.)
Attention: James G. Baumann, Jr.
P.O. Box 1220
Decatur, IL 62525

A barcode consisting of vertical bars of varying heights, located at the bottom of the document.

- #### 4. LEGAL BASIS FOR SUBMISSION

The RLD is Ativan®, Wyeth-Ayerst, NDA 18-140. There is no unexpired patent and no marketing exclusivity.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Lorazepam Injection, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original ANDA	December 12, 1996
Deficiency Letter	August 4, 1997
Amendment	August 27, 1997
Amendment	March 2, 1998
Amendment	June 9, 1998
Amendment	July 7, 1998

- 10.
- PHARMACOLOGICAL CATEGORY

Preanesthetic anxiolytic agent

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF
DMF
DMF

ANDAs 74-974 and 75-025 must be approved together because of the common insert.

- ### 13. DOSAGE FORM

- ## 14. STRENGTH

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75025

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620
Microbiologist's Review #2
March 10, 1998

A. 1. ANDA: **75-025**

APPLICANT: Taylor Pharmaceuticals (an Akorn Co.)
Attention: James G. Baumann, Jr.
Post Office Box 1220
Decatur, Illinois 62525

2. PRODUCT NAME: **Lorazepam Injection, USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: **0.2% (2 mg/mL)**
Sterile nonpyrogenic solution for intramuscular and
intravenous injection; packaged as a 1 mL fill in a 2 mL
glass vial

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: Used as a preanesthetic medication
in adult patients to produce sedation, relief of anxiety
and decreased ability to recall events related to the day
of surgery

6. PHARMACOLOGICAL CATEGORY: Anti-anxiety drug

B. 1. DATE OF INITIAL SUBMISSION: October 1, 1996
(Received by OGD on October 4, 1996) *as # 2/10/98*

2. DATE OF AMENDMENT: August 27, 1997

Subject of this Review (Received by OGD on August 28, 1997)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 3/10/98

Jul 21
C. REMARKS: The subject amendment is in response to the
microbiology deficiencies in the letter dated
August 4, 1997.

D. CONCLUSIONS: The submission is recommended for approval on
the basis of sterility assurance.

 /S/ 3/10/98
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate **ANDA**
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\75-025a
Initialed by R. Patel *initialed 3/10/98*

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75025

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-025

SPONSOR: Akorn, Inc.

DRUG: Lorazepam Injection (0.2%)

DOSAGE FORM: Injection

STRENGTH: 2 mg/mL

REFERENCE PRODUCT: Ativan® Injection, 2 mg/mL (Wyeth-Ayerst).

SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Lorazepam for injection, USP, 2 mg/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Ativan® Injection, 2 mg/mL (Wyeth-Ayerst).

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 6/5/97

GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 6/9/97

f DIRECTOR: Nicholas Fleischer, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 6/24/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

JUN 23 1997

Lorazepam Injection (0.2%)

2 mg/mL (1 mL/2 mL vial)

ANDA # 75-025

Reviewer: Z.Z. Wahba

File #75025w.d96

Akorn, Inc.

Decatur, IL

Submission Date:

December 12, 1996

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Lorazepam for injection, USP, 2 mg/mL (1 mL fill in a 2 mL vial). The reference listed drug (RLD) is Ativan® Injection, 2 mg/mL (Wyeth-Ayerst, NDA #18-140).
2. Lorazepam is a benzodiazepine with antianxiety and sedative effects. Lorazepam injections are intended for intramuscular or intravenous routes.

FORMULATION COMPARISON

Comparative compositions of the test and the reference (Ativan® Injection, 2 mg/mL, Wyeth-Ayerst Laboratories) products are as follows:

Ingredient	Test Product	RLD
Lorazepam ✓	2 mg/mL	2 mg/mL
benzyl alcohol, NF ✓	20 mg/mL (2.0%)	20 mg/mL (2.0%)
polyethylene glycol / 400	203 mg/mL (0.18 mL/mL)	0.18 mL/mL
propylene glycol ✓	q.s.	q.s.

COMMENTS

1. Composition of the test product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA.
2. The test product is a parenteral solution intended solely for administration by injection.
3. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Akorn, Inc. demonstrates that lorazepam injection solution, 2 mg/mL falls under 21 CFR Section 320.22(b)(1) of Bioavailability/Bioequivalence Regulations. The waivers of *in vivo* bioequivalence study requirements for the firm's lorazepam 2 mg/mL injection solution is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems Akorn's lorazepam injection solution, 2 mg/mL to be bioequivalent to the reference listed product, Wyeth-Ayerst's Ativan® Injection, 2 mg/mL.

The firm should be informed of the recommendation.

/S/
Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Concur: _____

/S/
fr Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Date: _____

5/9/97

6/23/97

cc: ANDA# 75-025, (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (Jallen), HFD-658 (Mhatre, Wahba), HFD-650 (Director), Drug File, Division File.

ZZWahba/050997/060597/file#75025w.d96

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75025

CORRESPONDENCE

21
C. Schofer

ANDA 75-025

Akorn, Inc.
Attention: James G. Baumann, Jr.
P.O. BOX 1220
Decatur IL 62525
llllllllllllllllllllllllllllll

JUN 25 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Lorazepam Injection USP, 2 mg/mL (1 mL/2 mL vial).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

fu N JS/ _____
Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Akorn

505(g)(2)(a)(vi)
Marie H. Winkler
1/30/97

December 12, 1996

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ABBREVIATED NEW DRUG APPLICATION
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2 mL vial)

Dear Madam or Sir:

In accordance with 21 CFR § 314.92 (a)(1), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Abbreviated New Drug Application for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial), an injectable drug intended for use in adult patients as a preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980. The suitability of the ANDA is documented in the submission.

This ANDA is contained in 4 volumes, and is organized in the manner recommended by the Office of Generic Drugs in its Policy & Procedure Guide 30-91. **At this time, Akorn requests approval for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial) manufactured according to the attached documentation, using Lorazepam, USP manufactured by _____ and components manufactured by _____** An expiration dating period of twenty four months is requested, based on the available three months stability data from stability batches stored at accelerated stability conditions.

This submission contains sterility assurance data. Akorn is providing sterility assurance information, including documentation for the sterilization process validation for lorazepam injection, in **Volumes 3-4**. This documentation is organized according to the directives presented in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (November, 1994).

RECEIVED
DEC 16 1996

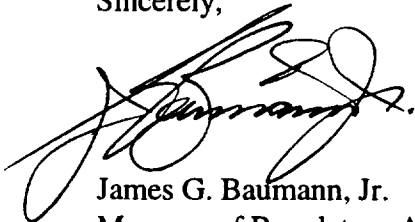
Akorn is filing an archival copy (in blue folder) of the ANDA, a technical review copy (in red folder), and a field copy sent to the Chicago district office (in maroon folder). The technical review copy and the field copies are identical to the archival copy and a

certification attesting to this is provided with the field copy. Four copies of the draft labeling are included in all copies of this ANDA.

In accordance with 21 CFR § 314.94 (d)(5), Akorn certifies that a true copy of this Abbreviated New Drug Application for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial) has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this application.

Should you have additional questions or if more information is needed, please do not hesitate to contact me at (217) 423-9715, or fax (217) 428-8514.

Sincerely,

A handwritten signature in black ink, appearing to read 'James G. Baumann, Jr.', with a stylized flourish at the end.

James G. Baumann, Jr.
Manager of Regulatory Affairs (Submissions)

Taylor Pharmaceuticals

an Akorn Co.

• generics • injectables • ophthalmics • contract services

August 27, 1997

AMENDMENT
W/AC

Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MAJOR AMENDMENT TO ANDA 75-025
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2 mL vial)

Dear Sir/Madam:

In accordance with 21 CFR § 314.96 (a)(3), and by reference § 314.60 (a), Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Major Amendment to ANDA 75-025 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial) an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980.

Akorn, Inc. would like to inform OGD that its manufacturing subsidiary has been renamed Taylor Pharmaceuticals, which was previously known as Akorn Manufacturing, Inc., as of August 21, 1996.

This amendment is in response to the FDA Major chemistry, labeling, and microbiology deficiency letter, dated August 4, 1997.

For ease of reference, this amendment is numbered sequentially in the lower right corner so that both the text and attachments bear consecutive numbers. A table of contents is provided for additional convenience of review.

Taylor is filing an archival copy consisting of one volume (blue folder) of this amendment and a technical review copy (red folder) which is identical to the archival copy. An additional certified copy (maroon folder) was sent to the Chicago District Office.

RECEIVED

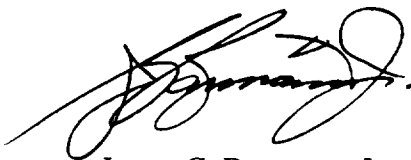
AUG 28 1997

GENERIC DRUGS

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Major Amendment to ANDA 75-025 for Lorazepam Injection, USP, 0.2%, has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as **Attachment M**.

Should additional information and/or clarification be required, please contact Laura Shotton, Regulatory Affairs Specialist, or me at (217) 423-9715, or FAX (217) 428-8514.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Baumann, Jr.', with a stylized flourish at the end.

James G. Baumann, Jr.
Manager, Regulatory Submissions

Taylor Pharmaceuticals

an Akorn Co.

• generics • injectables • ophthalmics • contract services

FA
11/12

July 7, 1998

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

JUL 07 1998

GENERIC DRUGS

RE: TELEPHONE AMENDMENT TO ANDA 75-025
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2 mL vial)

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Telephone Amendment to our Abbreviated New Drug Application ANDA 75-025 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial), an injectable drug intended for use in adult patients as a preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery.

This amendment is in response to a teleconference held on July 1, 1998 between FDA personnel (Joseph Buccine, Dr. Rashmikant Patel, Dr. Vilayat Sayeed, and Kathy Woodland) and Taylor Pharmaceuticals personnel (Jim Baumann, Lou Fraser, Rick Taylor, Charles Coates, and Dennis Roberts). FDA had previously requested (teleconference with Dr. Sayeed on June 23, 1998) that Taylor delete the potency adjustment step in the lorazepam batch records (ANDAs 74-974 and 75-025) together with the corresponding potency adjustment (fortification) worksheets.

After a brief discussion of the issue, the following responses are being provided as a follow-up to the teleconference:

1. Taylor will *delete* the manufacturing step that adjusts the Lorazepam, USP content of the solution, together with the corresponding potency adjustment worksheets from the master batch records as requested by FDA. During the teleconference, Dr. Patel specifically referenced page 000296, and pages 000299 and 000300 in *ANDA 74-974 (syringe)* as the manufacturing step and pages that should be deleted from the batch record. These changes are reflected on the revised master batch record pages (formulation procedure only) for

Lorazepam Injection, USP, 0.2% (vial) provided as *Attachment A*. Both the manufacturing step that would allow for a potency adjustment, together with the two (2) potency adjustment worksheets, have been deleted.

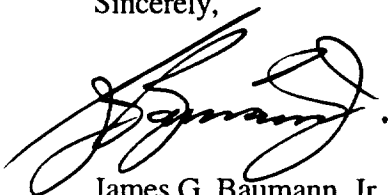
2. Should a potency adjustment be found necessary on future commercial batches, Taylor will provide a pre-approval supplement regarding potency adjustment as part of the post approval commitments referenced in 21 CFR § 314.70.
3. Per discussion and agreement, Taylor is providing a revised copy (*see Attachment B*) of the product specifications for lorazepam to reflect the following changes. *Please note that the revised manufacturing steps provided in Attachment A also reflect these changes.*
 - In-Process Specifications: Change lorazepam assay limits *from* %” to %” and
 - Finished Product Release Specifications: Change lorazepam assay limits *from* %” to ‘ %”.

Taylor is filing an archival copy consisting of one volume (in blue folder) of this amendment and a technical review copy (in red folder) which is identical to the archival copy. An additional certified copy (maroon folder) was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Telephone Amendment to ANDA 75-025 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial) has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as *Attachment C*.

Should you have additional questions, please feel free to contact me at your convenience at (217) 423-9715 or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

Taylor Pharmaceuticals

an Akorn Co.

• generics • injectables • ophthalmics • contract services

June 9, 1998

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

JUN 12 1998

GENERIC DRUGS

RE: TELEPHONE AMENDMENT TO ANDA 75-025
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2 mL vial)

ORIG AMENDMENT

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Telephone Amendment to our Abbreviated New Drug Application ANDA 75-025 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial), an injectable drug intended for use in adult patients as a preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery.

This amendment is in response to a teleconference held on June 2, 1998 between FDA (Joseph Buccine, Project Manager, OGD, and Kathy Woodland, Reviewing Chemist, OGD) and Taylor Pharmaceuticals (Jim Baumann, Mgr., Regulatory Submissions, and Dennis Roberts, Director of Research and Development). FDA indicated that there were some concerns about the limits Taylor had proposed for the degradation products listed in the product specification sheet for lorazepam. During the teleconference, Mr. Buccine indicated that Taylor could provide its response as a "Telephone Amendment".

After a brief discussion of the issues pertaining to the degradant limits, the following responses are provided as a follow-up to the teleconference:

1. Taylor will reduce the proposed degradation limit for *related compound D* (RC_D) *from* NMT % *to* NMT % [at release] and *from* NMT % *to* NMT % [shelf-life] in response to FDA's concern that the % limit was "to high" in view of the current stability results and by comparison to what was already being marketed in the field. Taylor will also reduce the proposed limits for *the individual lorazepam degradants/impurities* *from* NMT % *to* NMT % [at release] and *from* NMT % *to* NMT % [shelf-life] in

response to FDA's concerns. These changes are reflected in the updated product specifications for Lorazepam Injection, USP, 0.2% (vial) provided as **Attachment A**.

2. FDA has requested that Taylor add a statement to the product specifications indicating that the Label Claim or Target, Finished Product, and Stability conforms to the requirements of USP <1> *injections*. Taylor has complied with this request and has updated the product specifications accordingly (*see Attachment A*). This statement will be included in all future C of As. Taylor's specifications are designed to comply with the requirements.
3. FDA has requested that Taylor reduce the limit on the individual impurities in the drug substance specification to reflect a value of *less than* the % proposed. The results of the API chromatographic purity testing was reviewed for individual impurities and related compounds. Results below 0.5% were reported for individual impurities and related compound D. The Active Pharmaceutical Ingredient Specification was updated (**Attachment B**) to include NMT % for individual impurities and RC_D. The results for related compound C (RC_C) did not justify the changes below %. A statement indicating limits of NMT % for (RC_C) was added to the specification (*see Attachment B*). This specification is consistent with the Finished Container limit for this impurity.

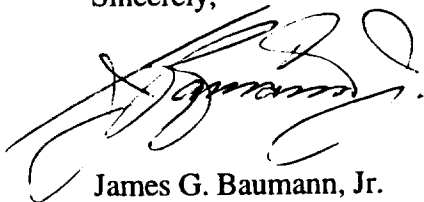
In addition to the above information, Taylor is providing updated stability data (24 month test results) on Taylor's drug product and the RDL, Ativan[®], as **Attachment C**. During the conversation, Mr. Buccine indicated that Taylor should provide its response as a "Telephone Amendment".

Taylor is filing an archival copy consisting of one volume (in blue folder) of this amendment and a technical review copy (in red folder) which is identical to the archival copy. An additional certified copy (maroon folder) was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Facsimile Amendment to ANDA 75-025 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL vial) has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as **Attachment D**.

Should you have additional questions, please feel free to contact me at your convenience at (217) 423-9715 or FAX (217) 423-5206.

Sincerely,

A handwritten signature in black ink, appearing to read "James G. Baumann, Jr.", with a stylized flourish at the end.

James G. Baumann, Jr.
Manager, Regulatory Submissions